PCT/US00/24232

10/069929

Eur päisches Patentamt | Eur pean Patent Office | Office eur péen des brevets

US00/24232

4

Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99307041.6

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE,
LA HAYE, LE 10/10/00

Eur päisches Patentamt
Eur pean Patent Office
Office eur péen des brevets

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 99307041.6

Anmeldetag:
Date of filing: 03/09/99
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
SCHOOL OF PHARMACY, UNIVERSITY OF LONDON
London WC1N 1AX
UNITED KINGDOM

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Degradable polymers

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
A61K47/48, C08G65/329, C08G65/332, C08G65/333

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du depôt:

Bemerkungen:
Remarks:
Remarques:

D gradable Polymers

The present invention is concerned with the production of degradable polymers and the production of materials therefrom and drug targeting using polymer-bioactive conjugates.

Background of the Invention

Covalent conjugation of a drug to a soluble, biocompatible polymer can result in improved efficacy of the drug. Compared to the free, unconjugated drug, polymer-drug conjugates exhibit this improvement for the following main reasons: (1) altered biodistribution, (2) prolonged circulation, (3) release of the drug in the proteolytic and acidic environment of the secondary lysosome after cellular uptake of the conjugate by pinocytosis and (4) more favourable physicochemical properties imparted to the drug due to the characteristics of large molecules (e.g. increased drug solubility in biological fluids).

For the treatment of cancer there are marked improvements in therapeutic efficacy and site specific passive capture through the enhanced permeability and retention (EPR) effect. The EPR effect results from enhanced permeability of macromolecules or small particles within the tumour neovasculature due to leakiness of its discontinuous endothelium. In addition to the tumour angiogenesis (hypervasculature) and irregular and incompleteness of vascular networks, the attendant lack of lymphatic drainage promotes accumulation of macromolecules that extravasate. This effect is observed in many solid tumours for macromolecular agents and lipids. The enhanced vascular permeability will support the great demand of nutrients and oxygen for the rapid growth of the tumour. Unless specifically addressed for tumour cell uptake by receptor-medicated endocytosis, polymers entering the intratumoural environment are taken up relatively slowly by fluid-phase pinocytosis.

Polymer-drug conjugates are a subset of a class of compounds known as "Polymer Therapeutics". Copolymers of hydroxypropyl methacrylamide (HPMA) have been extensively studied for the conjugation of cytotoxic drugs for cancer chemotherapy. An HPMA copolymer conjugated to doxorubicin known as PK-1, is currently in Phase II evaluation in the UK. PK-1 displayed reduced toxicity compared to free doxorubicin in the Phase I studies. The maximum

tolerated dose of PK-1 was 320 mg/m^2 (dox equivalent) which is 4-5 times higher than the usual clinical dose of free doxorubicin.

The three main parts of a polymer-drug conjugate: (1) polymer, (2) linker and (3) conjugated drug all have defined biological function. Together these components produce a distinct profile of pharmacological, pharmacokinetic and physicochemical properties typical of polymer-drug conjugates. The polymer is not a mere carrier for the pharmacologically active drug. The properties of the polymer are directly responsible for defining the circulation half-life, rate of cellular uptake, minimising toxicity of potent cytotoxic drugs and imparting favourable physicochemical properties (e.g. increasing the solubility of lipophilic drugs).

Lysosomes also contain a vast array of hydrolytic enzymes including proteases, esterases, glycosidases, phosphates and nucleases. Drugs have been conjugated to polymers using conjugation linkers that degrade in the lysosome while remaining intact in the bloodstream. Since many drugs are not pharmacologically active while conjugated to a polymer, this results in drastically reduced toxicity compared to the free drug in circulation.

An increasing number of soluble polymers have been used as macromolecular partners for pendent chain drug conjugation. Many of thes polymers have been extensively studied and can be organised into 2 broad classes: (1) nondegradable synthetic polymers and (2) potentially degradabl synthetic polymers and natural polymers. In the past many polymers used for conjugation were selected because they were water soluble and biocompatibl , e.g. did not bind blood proteins and were non-immunogenic.

The synthetic polymers PEG and HPMA copolymers have been extensively studied as polymeric drug carriers. These polymers are hydrophilic and are well tolerated in man, but their main disadvantage is that the polymer backbone is not biodegradable *in vivo*. Only polymers of molecular weight lower than the renal threshold can be used for systemic administration. It is imperative that the systemic use of non-degradable polymers such as HPMA copolymers, PEG and PVP is limited to molecules of a molecular weight which are readily cleared, otherwise long-term deleterious accumulation in healthy tissue could result.

Some polysaccharides have the advantage of being enzymatically biodegradable, e.g. dextran, and can therefore be administered over a wider molecular weight range without the fear of prolonged accumulation in the body. However, polysaccharides lack structural uniformity and exhibit the propensity upon chemical modification (i.e. drug conjugation) to become immunogenic or nondegradable. Other potentially degradable soluble polymers have been prepared from amino acids (e.g. poly(glutamic acid), poly[^{5}N-(2-hydroxyethyl)-L-glutamine) (PHEG), β-poly(2-hydroxyethyl aspartamide) (PHEA), poly(L-glutamic acid) and polylysine. Other polymers and copolymers including pseudo-poly(amino acids) and polyesters such as poly(α or β-malic acid), and block copolymers such as PEG-lysine and poly(lysine citramide) have been also been investigated for drug conjugation. In principle, proteins can also be used to conjugate drugs and albumin continues to be actively investigated as a macromolecule candidate for drug conjugation. The major limitations for using proteins compared with synthetic polymers to conjugate drugs include an increased propensity for inducing immunogenicity, denaturation and nonspecific degradation. None of the potentially degradable polymers have suitable chemical structural characteristics which would allow greatly enhanced degradation at pH 5.5.

The synthesis of unsaturated polyesters from di-potassium salts of cis-aconitic acid, itaconic acid, mesaconic acid and 1,4-dibromobutane has been described (Sepuchre, M.O. *et al*, Macromol. Symp., 122 (International Symposium on Polycondensation, Related Processes and Materials, 1996), 291-296 (English) 1997). The polycondensation of the cis-aconitic acid salt was accompanied by a decarboxylation reaction.

A wide variety of linkages have been used to covalently bind a drug to the polymeric carrier. Several examples include, amide, ester, hydrazide, urethane, carbonate, imine, hydroxyl, thioether, azo and C-C.

Following the concept of lysosomotropic drug delivery two broad classes of pendent chain linkers have emerged as the main focus of research over the last two d cades. Thes are:

1. Peptidyl linkers designed to be stable in th blo dstream, but degradable by lysosomal enzymes and thus able to rel ase the drug intracellularly.

2. Acid-labile, pH dependent linkers which are designed to remain stable in plasma at neutral pH (7.4), but release drug intracellularly by hydrolysis in the more acidic environment of the endosome and lysosome (pH 5.5 to 6.5).

Peptide linkers have been shown to mediate lysosomotropic drug delivery (wherein the drug preferentially accumulates in the lysosome). It has become apparent that one of the successful methods of control of the rate and location of drug release from pendent chain polymers has occurred favourably when a drug is bound to the polymer backbone via a peptidyl side-chain.

Since the discovery that peptidyl side chains in HPMA copolymers could be designed for cleavage by model enzymes such as chymotryspin, tryspin and papain recent studies have seen the systematic development of HPMA copolymer-anticancer conjugates. These contain peptidyl linkers tailored for cleavage by lysosomal proteases. Such linkers have now become more widely used in many different polymer conjugates.

The relatively low pH within the endosomal, and lysosomal compartments and the observation that the extracellular, interstitial environment in some tumours is also acidic, has inspired the development of pendent chain linkers that hydrolytically degrade more quickly at pH values less then 7.4. *Cis*-aconityl acid and Schiff base derivatives are the two predominant types of hydrolytically labile linkers that have been explored.

Shen and Ryser (*Biochim, Biophys. Res. Commun.*, **1981**, 102, 1048-1054) disclose pH-sensitive linkers of n-cis-aconityl and n-maleyl groups used to conjugate daunomycin to amino ethyl polyacrylamide and to poly(d-lysine). Hydrolysis of the cis-aconityl spacer released daunomycin from poly-(d-lysine) in the lysosomes.

Diener, *et al (Science,* **1986**, 231, 148-150) have shown that daunomycin, when conjugated to a targeting antigen by a cis-aconityl spacer, remains inactive in the extracellular system, but becomes active after cleavage within th acidic lysosomal environment of a target cell.

Dilman, *et al* (*Cancer res.*, **1988**, 48, 6097-6102) have conjugat d daunorubicin to th anti-T-cell monaclonal antibody T101 using a cis-aconityl group. The pH sensitivity of the linkage was confirm d. A similar

study using a monaclonal antibody conjugated to doxorubicin has been shown to suppress the growth of established tumour xenografts in nude mice (Yang and Ricefelt *Proc. Natl. Acad. Sci.*, **1988**, 85, 1189-1193).

GB 2,270,920 discloses a therapeutically useful alginate-bioactive agent conjugate, wherein the alginate and bioactive agent are connected covalently via an acid labile linkage, preferably a cis-aconityl group.

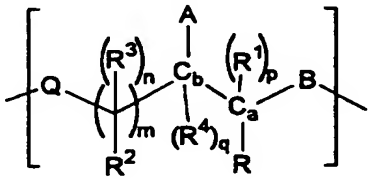
An advantage of conjugating a drug via an acid-labile linker is that free drug alone can be released from the pendent chain rather than amino acid or peptide drug derivatives which can occur with peptidyl linkers.

One object of the present invention is to provide pH dependant degradeable polymers.

A further object of the present invention is to degradable polymers that degrade in the endosome or lysosome,provide while enabling conjugation to a lysosomally labile bioactive agent.

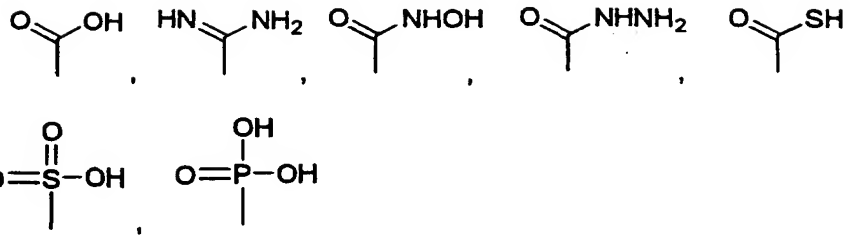
Summary of the Invention

One embodiment of the invention provides a polymer comprising: a polymeric backbone comprising at least one unit having the structure (I),

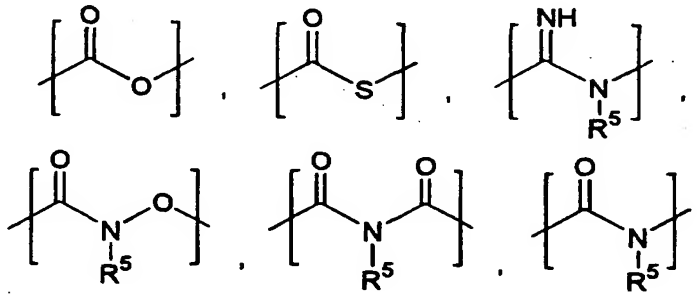


(I)

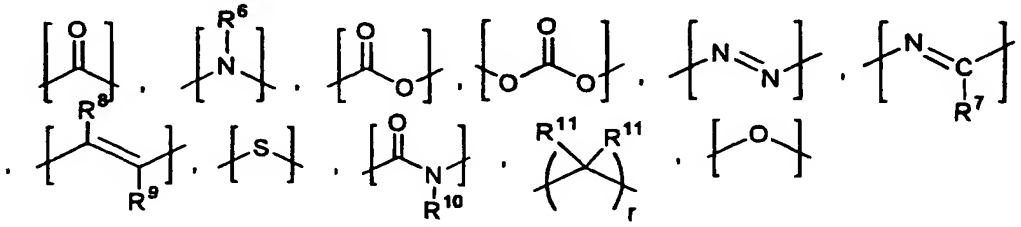
wherein R-R^4 comprise groups selected from the group consisting of H, C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl or any of the group consisting of C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms; R and R^2 or R and R^4 or R and R^1 or R^2 and R^3 may be joined so that with the carbon atom(s) to which they are attached they together form a saturated, partially unsaturated or unsaturated ring system respectively, may hav a pendent group which may incorporate a linker unit, (for exampl a peptide linkage) or a unit having the structure (I); A comprises a proton donating moiety selected from the group consisting of



B comprises a hydrolytically labile group and is selected from the group consisting of



wherein each R^5 is individually selected from the group consisting of H, C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl; wherein groups A and B are in a cis-configuration about bond C_a-C_b; m is an integer of 0 to 100, n, p and q are each an integer of 0 or 1; Q comprises 1 or more structures selected from the group consisting of



wherein R^6-R^{11} are individually selected from the same group as defined for group R above and r is an integer between 1 and 5000, preferably 1 to 10, most preferably 1 to 6.

C_a-C_b may be a double bond, in which case p and q are 0 and groups A and B are in a cis-configuration across the double bond. R and R^2 or R and R^4 or R and R^1 or R^2 and R^3, preferably R and R^2, may be join d to oneanother to form part of a C_3 - C_{12} ring system which may have none one or mor than one unsaturat d bond and may be aromatic. Wh n such a ring system is formed and C_a -C_b is not a double bond, A and B ar in a cis-

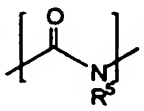
configuration about bond C_a -C_b. Preferably such a ring system is a C_3-C_7 ring system. The ring system may incorporate any of the groups defined for R or may include one or more Q groups.

When C_a -C_b is a single bond, p and q are 1 and R, R^1, R^4 and A are selected from sterically bulky groups in such a way as to maintain a cis-configuration of A and B about bond C_a -C_b. Preferably C_a-C_b is a double bond.

Preferably R-R^4 are individually selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, pentyl and hexyl and isomers thereof, acyl, alkoxy and acyloxy or mixtures thereof. Most preferably R, R^2 and R^3 are hydrogen.

Preferably each R^5 is individually selected from the group consisting of H, methyl, ethyl, propyl, butyl, pentyl and hexyl, preferably hydrogen.

A preferably comprises a group or a protected carboxylic acid group.

B preferably comprises an amide bond, and is most preferably a group,  wherein R^5 has been hereinbefore defined.

Q may comprise more than one or a mixture of the structures defined above. Preferably Q comprises a carbonyl group, -NR^{12}-, -O- or -CH_2- group, wherein R^{12} is selected from the group consisting of hydrogen, C_{1-6}-alkyl, preferably methyl, ethyl, propyl, butyl, pentyl and hexyl and isomers thereof. Preferably R^{12} is a hydrogen atom.

Most preferably Q comprises a carbonyl functionality.

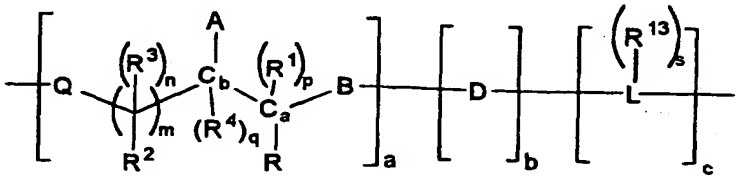
In a particularly preferred embodiment bond C_a-C_b is a double bond, R is hydrogen, R^2 and R^3 are hydrogen, n is 1, m is 1, p and q are 0, A is a carboxylic acid group, B comprises an amide bond and Q comprises an carbonyl group.

Preferably where the polymer contains more than one (I) moiety, the groups A, B, Q, R-R^4, m, n, p and q in each individual moiety are the same.

The other components of the polymeric backbone may be other groups having the structure (I), peptide units or other degradeable polymeric, oligomeric or monomeric units. For example, the polymeric backbone may comprise acrylic polymers, alkylene polymers, urethane

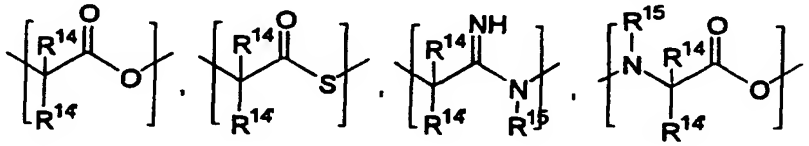
polymers, amide polymers, polypeptides, polysaccharides and ester polymers. Preferably the backbone components comprise derivatised polyethyleneglycol or copolymers of hydroxyalkyl(meth)acrylamide, most preferably amine derivatised polyethyleneglycol or hydroxypropylmethacrylamide-methacrylic acid copolymers, or derivatives thereof.

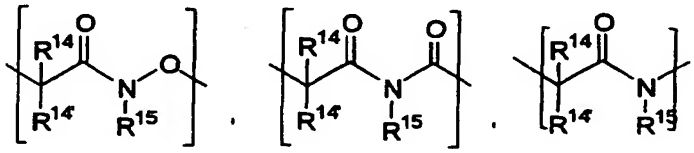
A further embodiment of the present invention provides a polymer comprising a polymeric backbone comprising the structure (II)



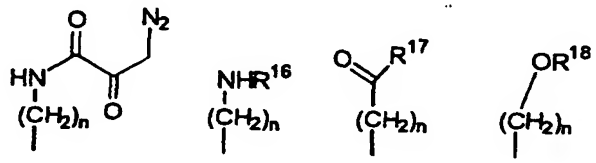
(II)

wherein A, B, Q, R-R^4, m, n, p and q are as defined above; L is a polymeric, oligomeric or copolymeric bridging group which comprises groups selected from the group consisting of acrylic polymers, alkylene polymers, urethane polymers, polyethylene glycols, polyamides(including polypeptides), polysaccharides and polyesters. a is an integer of 1 to 100000, b and c ar integers of 0 to 100000 and s is an integer of 0 to 100; D comprises one or more structures individually selected from the group consisting of,





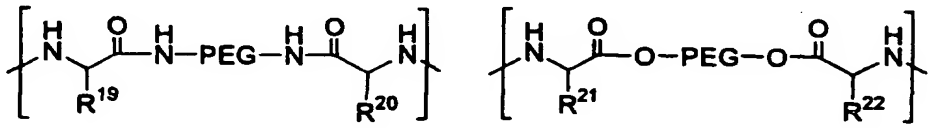
wherein R^{14} and R^{14a} comprise groups individually selected from the same groups as defined for R or may comprise a structure selected from the group consisting of

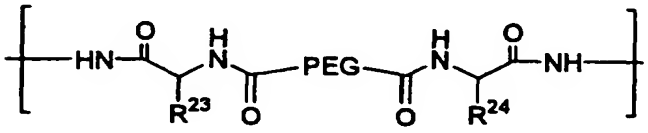


wherein n is an integer of 0-100, R^{15} is selected from the group consisting of hydrogen and C_1-C_6 alkyl, R^{16} to R^{18} are individually selected from the group consisting of H, C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_5-C_{18} cycloalkyl or is selected from the group consisting of C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms, a pendent group comprising a linker unit, for example a peptide linkage or a unit having the structure (I) or a leaving group; R^{13} is selected from the group consisting of H, C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_5-C_{18} cycloalkyl or is selected from the group consisting of C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms, R^{13} may contain a linker unit, for example a peptide linkage or a unit having the structure (I).

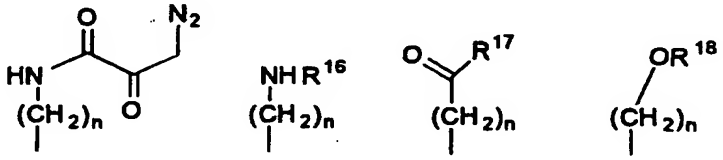
Preferably L comprises a compound selected from the group comprising derivatised polyethyleneglycol and (hydroxyalkyl(meth)acrylamide-methacrylic acid copolymer or amide or ester derivative thereof, most preferably amine derivatised polyethyleneglycol.

Most preferably L comprises a structure comprising a group selected from the group consisting of





wherein PEG is polyethyleneglycol, R^{19}-R^{24} may be a pendent group comprising a cleavable linker unit, and comprise groups individually selected from the same groups as defined for R or may comprise a structure selected from the group consisting of



wherein n and R^{16} to R^{18} have been defined hereinbefor .

s is preferably an integer of 1 to 10.

Where L is a group incorporating one of groups R^{19} to R^{24}, b is preferably 0.

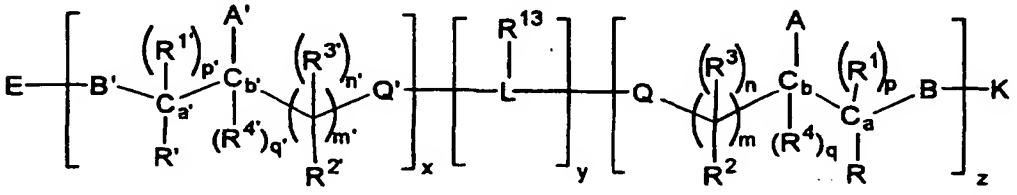
Preferably at least one of R^{14} to R^{24} should incorporate a pendent group. Preferably such a pendent group incorporates a cleavable bond. This would be the case wherein R^{14} to R^{24} comprise a cleavable group (I) as hereinbefore defined, or a peptidic bond capable of being cleaved by lysosomal enzymes.

Preferably R^{16}-R^{18} are H, tosylate, Fmoc, halogen, methyl, ethyl, propyl, butyl, pentyl or isomers thereof.

A pendent group as defined hereinbefore may incorporate a bioactive agent to form a conjugate. Preferably the bioactive agent is an anti-cancer agent, for example doxorubicin, daunomycin, taxol and the like. This permits both cleavage of the linker unit, thus releasing drug to the desired site, and biodegradation of the macromolecular carrier, thus reducing side effects associated with the difficulty of clearing such molecules from the system.

Preferably the molecular weight of L is less than 220 kDa, more preferably less than 100 kDa, most preferably less than 30 kDa. Preferably the polymer has a weight of 500D-400 kDa.

A further embodiment of the invention provides prepolymer comprising the structure (III)

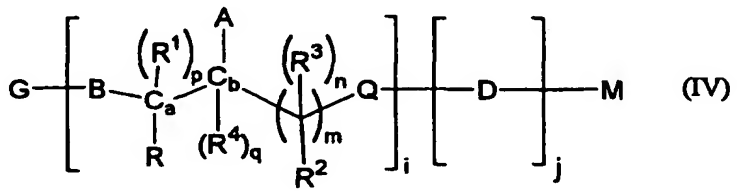


(III)

wherein A, B, Q, R-R^4, R^{13}, L, m, n, p and q are as defined herein before; A', B', Q' $R^{1'}$-$R^{4'}$, m', n', p', and q' are selected from the groups as defined for A, B, Q, R^1- R^4 m, n, p and q respectively; E and K are selected from the group consisting of hydrogen, a protecting group or an activating group and may be the same or different; z is an integ r of of 1 to 100, y is an integer of 0 to 10 and x is an integer of 0 to 100.

z is preferably 1, y is preferably 1 or 0, x is preferably 1 or 0. Most preferably x=z. Preferably B=B', Q=Q', A=A', R^1-R^4=$R^{1'}$-$R^{4'}$, m=m', n=n', p=p' and q=q'. Preferably when B and/or B' comprise a carboxylic acid group, E and K are an activating group selected from the group consisting of N-succinimidyl, pentachlorophenyl, pentaflourophenyl, para-nitrophenyl, dinitrophenyl, N-phthalimido, N-norbornyl, cyanomethyl, pyridyl, trichlorotriazine, 5-chloroquinolino. These groups are formed from the reaction with group B, with the following compounds N-hydroxysuccinimide, pentachlorophenyl, pentaflourophenyl, para-nitrophenyl, dinitrophenyl, N-hydroxyphthalimide, N-hydroxynorbornene, cyanomethyl, hydroxypyridine, trichlorotriazine, 5-chloro-8-hydroxy-quinoline respectively. In this embodiment, groups E and K are known as an "active esters ". Preferably E and K are N-succinimidyl. There are other activating moieties that can act as an acylation reagent, such as the mixed anhydrides.

A further embodiment of the present invention provides a prepolymer comprising the structure (IV)



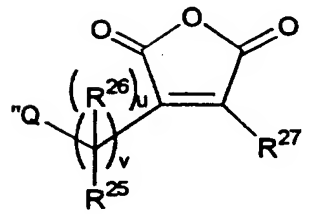
(IV)

wherein A, B, Q, R-R^4, D, m, n, p and q are as defined above, G and M are selected from the group consisting of hydrogen, an activating group or a protecting group and may be the same or different, i and j are integers of 1 to 10.

i is preferably 1 and j is preferably 1.

Preferably when B and/or D comprise a carboxylic acid group, G and M are an activating group as defined above. Preferably G and M are hydrogen or N-succinimidyl.

A further embodiment provides process for preparing a polymer, copolymer or prepolymer comprising reacting at least one compound having the structur (V)



(V)

wherein R^{25}, R^{26} and R^{27} are selected from the group as defined for R; Q" is selected from the group consisting of carboxylic acid, primary or secondary amine and carbonyl; u is an integer of 0 or 1, v is an integer of 1 to 100, R^{27} and R^{25} may be attached to form part of a C_3 - C_{12} ring system which may have more than one unsaturated bond and may be aromatic; with at least one compound selected from the group consisting of J and $R^{13}LNHR^{28}$, wherein L and R^{13} groups are as defined above and R^{28} is selected from the same group as defined for R and may be the same or different, J is a compound having at least one primary or secondary amine and a carboxylic acid group and a pendent group incorporating a cleavable bond.

Preferably Q" is a carboxylic acid group; R^{27} is hydrogen, u and v ar 1, R^{25} and R^{26} are hydrogen or methyl. Most preferably $R^{13}LNHR^{28}$ comprises a NHR^{29} group, wherein R^{29} is individually selected from the same group as defined for R^{28}.

A further embodiment provides a method of selectively degrading a polymer comprising the steps of:

a) introducing a polymer as defined by structure (I) or (II) to an environment having a pH of less than 6.5,

b) cleaving said polymer.

A further embodiment provides a method for releasing a bioactive agent comprising the steps of

a) introducing a conjugate as described hereinbefore to an environment having a pH of less than 6.5,

c) cleaving the bioactive agent from the linker group by acid or enzymic hydrolysis,

d) optionally additionally cleaving th polymer by acid or enzymic hydrolysis.

The present invention also comprises compositions which comprise at least one polymer or polymer-bioactive agent conjugate and a carri r. In the

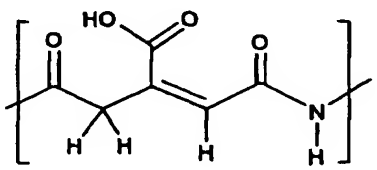
case of *in vivo* treatment it is envisaged that the compositions may be administered orally, by injection, or topically and may comprise a pharmaceutically acceptable excipient.

A further embodiment of the invention includes the use of the novel polymer as a pharmaceutical excipient. As it degrades very quickly at low pH ranges it has application as an excipient for drug formulations prepared for oral administration (i.e. for rapid degradation in the gut or gastro intestinal tract where there are regions of very low pH).

The novel polymers of the present invention may be water soluble or insoluble depending on size and the nature of its components. The degradation products of the polymer are preferably soluble.

Detailed Description of the Invention

In one embodiment, the present invention provides a polymer comprising an acid labile, pH dependent backbone incorporating a cis-aconityl group therein, more specifically a group having the structure (VI). This group is designed to remain stable in plasma at neutral pH (~7.4), but degrade intracellularly by hydrolysis in the more acidic environment of the endosome or lysosome (~pH 5.5 - 6.5).

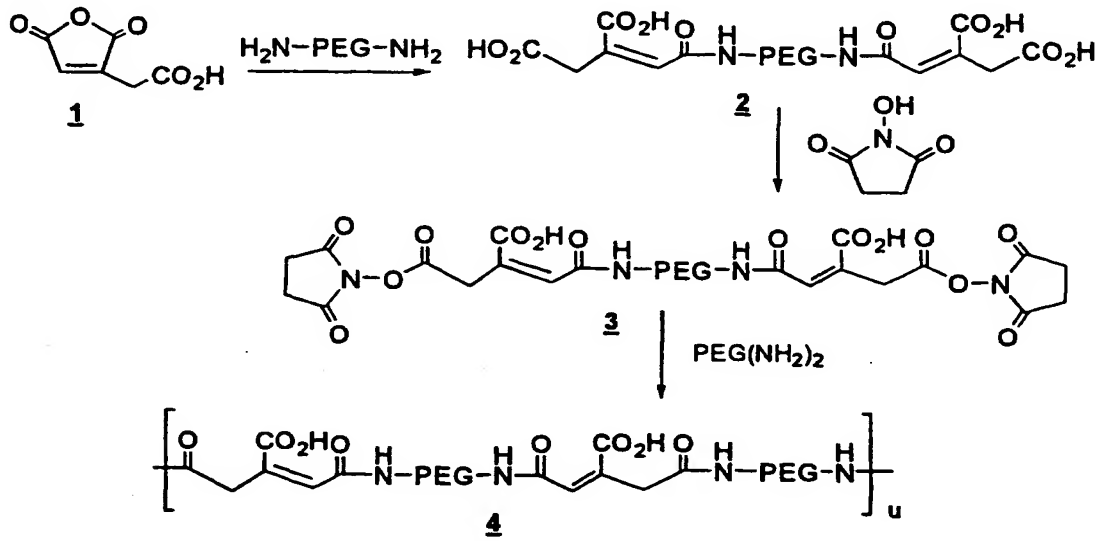


(VI

Preferably the group (VI) is incorporated into a polymer backbone comprising a polymeric, oligomeric or copolymeric group which comprises functionalised or unfunctionalised polyethyleneglycol, ethyleneglycol copolymers, poly(hydroxyalkyl(meth)acrylamide), for instance hydroxypropylmethacrylamide-methacrylic acid copolymer (or amide or ester derivative thereof) and copolymers of styrene and maleic anhydride, polyurethanes, polyalkylenes and polyamides or amino acid residues. In a particularly preferred embodiment the polymeric backbone should incorporat a functionalised poly thyleneglycol (PEG) polymer or copolymer most preferably an amine functionalised PEG polym r.

The molecular weight of the polymer of the present invention is in the range of 30-400 kDa, while the weight of the prepolymer (III) is preferably less than about 220 kDa in order to ensure that the degraded polymer subunits are cleared from the lysosome and the kidney glomerulus. Most preferably the polymer degradation products have a molecular weight in the range of 0.5 kDa-30 kDa.

One preferred polymer of the present invention is a water soluble polyamide having the formula 3 and is made by the general reaction schem summarised below:

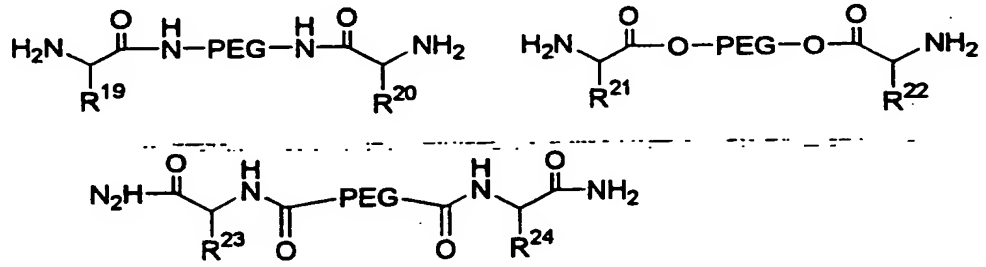


wherein PEG is a polyethylene glycol group having a molecular weight in the range 500 Da-100kDa or derivative thereof and u is an integer in the range of 1-10000.

As shown above, the preferred polymer may be prepared by a 2 step, and optionally 3 step process. In the first step an equivalent of cis-aconitic anhydride, 1, is reacted with a compound containing two primary or secondary amine groups.

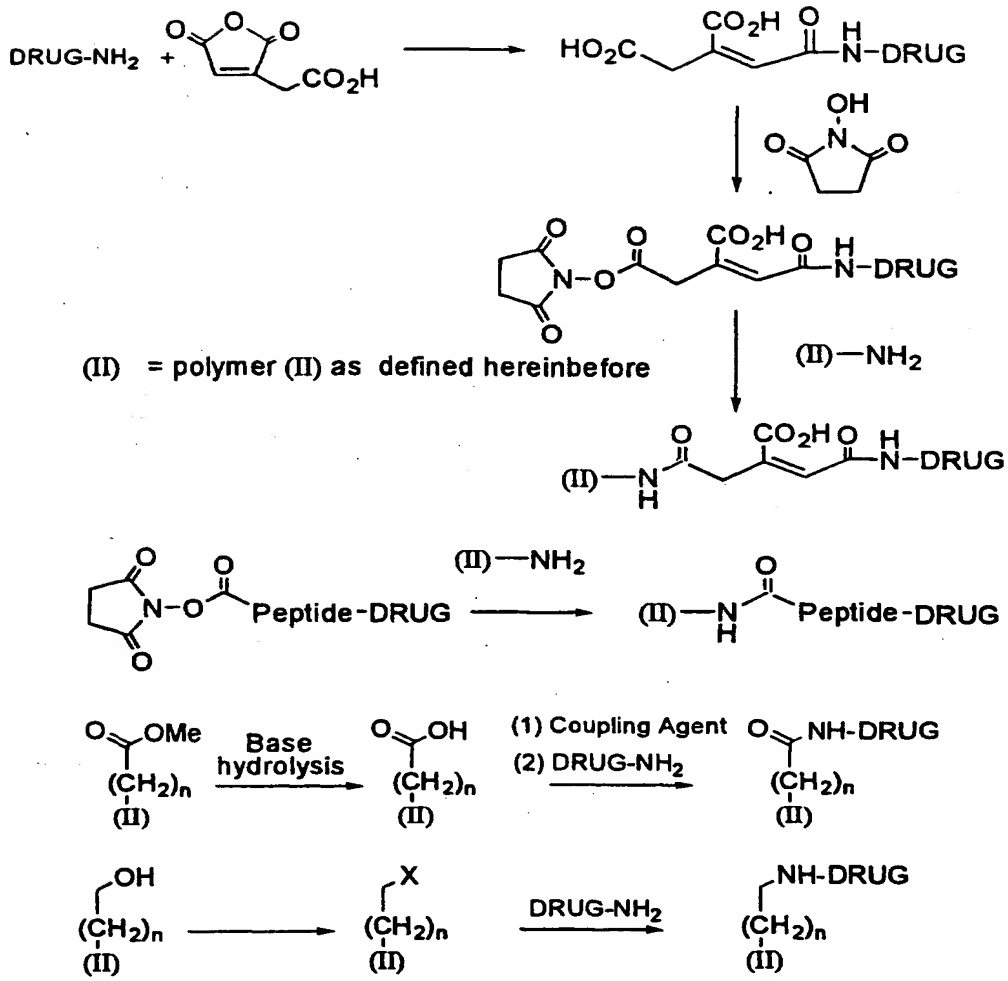
Suitable solvents include non-protic solvents including acetonitrile, dimethylformamide, dimethylsulphoxide, DMA, tetrahydrofuran, ethyl acetate, dioxane, acetone etc. Preferably acetonitrile is used. The product is isolated by a suitable method such as solvent separation and the resultant macromonomer 2 is then used as a prepolymer for the production of the acid labile polymer backbone.

Macromonomer (2) may be reacted with two equivalents of an activating group as described hereinbefore (N-hydroxysuccinimide shown) to produce an active monomer. The reason for this is that the unprotected carboxylic acid moieties would otherwise compete in the polymerization reaction, resulting in potential incomplete degradation of the polymer backbone. This situation could, however, be used in the production or enablement of cross-linking and gel formation. If protection is carried out as shown, compound 3 is produced. This compound (3) or compound 2 may then be reacted further with a compound $R^{13}LNHR^{28}$ as defined hereinbefore. In the diagram shown, $R^{13}LNHR^{28}$ is simply a amine-difunctionalised PEG molecule. Other compounds that are suitable for use as $R^{13}LNHR^{28}$ are



wherein R^{19}-R^{24} have been defined hereinbefore. Preferably the above defined R^{14}-R^{19} groups contain a group that is capable of conjugation to a drug, or a precursor thereof, for example, the group R^{19}-R^{24} should preferably contain a primary or secondary amine.

Suitable methods of attaching a linker molecule or a drug to the polymer backbone are as follows:



Wherein x is a leaving group such as tosylate, Br and the like.

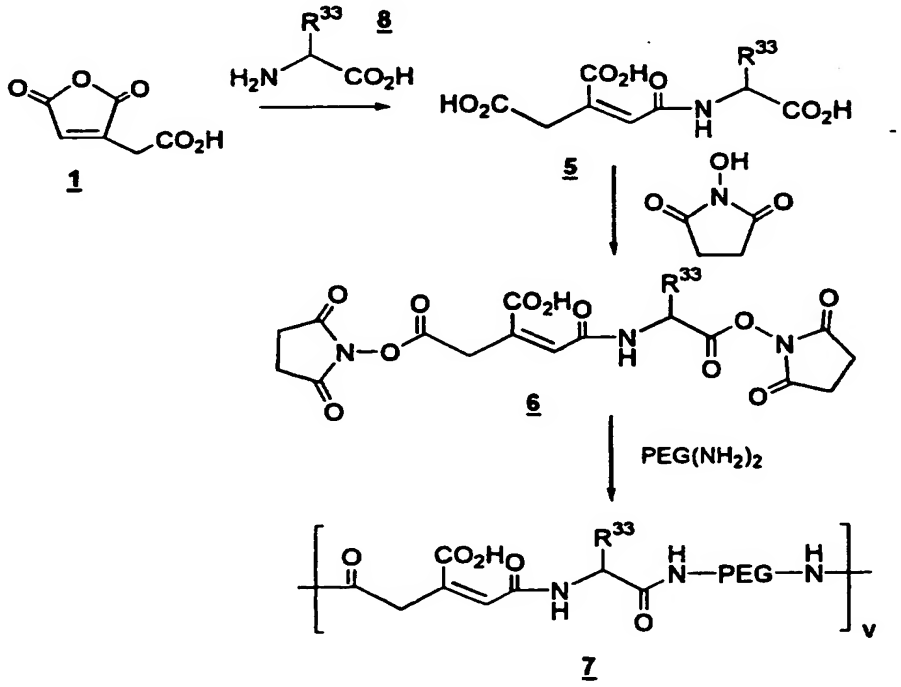
The reaction of compound **2** or **3** results in one of the preferred polymers of the present invention, compound **4**.

The conditions for the step to the final product **4** of the reaction are different than the first, and involve the use of a condensation or coupling reagent type of compound such as a carbodiimide (e.g. dicyclohexyl carbodiimide, diisopropylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, mixed anhydride reagents (e.g. 2-ethoxy-1-ethoxycarbonyl-1-1, 2-dihydroquinoline, 2-isobutoxy-1-isobutoxycarbonyl-2, 2-dihydroquinoline, isobutyl chloroformate), phosphonium salts (.g. benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate (Castro's reagent), bromo-tris-pyrrolidino-phosphonium hexafluorophospate, benzotriazole-1-yl-oxy-tris-pyrrolidino-

phosphonium hexafluorophosphate), uronium salts (e.g. 2-(1H-benzotriazole-1-yl)-1,2,3,3,-tetramethyluronium hexafluorophosphate, 2-(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborate) and carbonates (e.g. 1,1'-carbonyl-diimidazole, N,N'-disuccininimidyl carbonate).

The particularly preferred solvents and conditions for this reaction are that molecule **2** is allowed to react in acetonitrile (with DIPC and hydroxysuccinimide) to give the macromonomer **3**. The macromonomer **3** is isolated then allowed to react in aqueous carbonate (Na_2CO_3) at pH 9, 24 h at ambient temperature to give the polymer such as **4**.

Another particularly preferred embodiment of the present invention is the production of the water soluble polyamide having the formula **7** and is made by the general reaction scheme summarised below:



7

wherein PEG is a polyethylene glycol group having a molecular weight in the range 500 Da-100kDa or derivative thereof, and v is an integer in the range of 1-10000. As with compound **4**, the preferred polymer may be prepared by a 2 step, and optionally 3 step process. In the first step an equivalent of cis-aconitic anhydride, **1**, is react d with a compound containing an amine group and a carboxylic acid group (**8**) wherein R^{33} is selected from the same group of compounds as defined for R^{19}-R^{24}.

Suitable solvents again include non-protic solvents, preferably acetonitrile. Macromonomer (2) may be reacted with two equivalents of a protecting group (N-hydroxysuccinimide shown) to produce an active monomer. If protection is carried out as shown, compound 6 is produced. This compound (6) or compound 5 may then be reacted further with a compound $R^{13}LNHR^{28}$ as defined hereinbefore. In the diagram shown, $R^{13}LNHR^{28}$ is simply a amine-difunctionalised PEG molecule. Other compounds that are envisaged for use as $R^{13}LNHR^{28}$ are as shown above.

Brief description of the drawings:

Figure 1 shows the degradation study of the preferred polyamide of the invention at pH 7.4, 5.5 and 2 in phosphate buffer at 37°C as described in the Examples.

Examples

Example 1

A 50 ml three neck round bottom flask was fitted with a condenser, thermometer and a dropping funnel. The flask was cooled using a water ice bath and PEG_{NH2} 500 Jeffamine (1.6 g, 3.2 mmol, 1 eq.) and acetonitrile (5.0 ml) were added to the flask. To the dropping funnel was added *cis*-aconitic anhydride 1 (2.0 g, 12.8 mmol, 4.0 eq.) and acetonitrile (10 ml). Under nitrog n atmosphere, the *cis*-aconitic anhydride solution was slowly added over a 30 minute period to the Jeffamine solution which turned a light yellow colour during the addition. The reaction was exothermic and the risk of possible decarboxylation was minimised by ensuring that the temperature of the reaction mixture remained in the range of 0-3 °C through out the addition of the anhydride solution. The ice water bath was the removed and the reaction mixture allowed to stir for 1 hour at ambient temperature. Diethyl ether (30 ml) was then added to the solution and the reaction mixture poured into a separatory funnel. More ether was added and the macromonomer 2 separated as an oil which settled to the bottom of the separatory funnel and was isolated. Excess solvent was first evaporated from the crude macromononer 2 under flowing nitrogen and then the oil dried in vacuum at 40 °C.

Preparation of polyamide 4.

To a solution of macromonomer **2** (0.73 g, 0.913 mmol) and N-hydroxysuccinimide (0.21 g,1.826 mmol) in methanol (15.0 ml) at 0 °C (cooled by ice water bath) was slowly added diisopropylcarbodiimide (0.38g , 1.826 mmol). The ice bath was removed and the red coloured reaction mixture stirred at ambient temperature for 2 h. Diethyl ether was then added to the reaction mixture to oil out the activated bis-NHS ester which was collected using a separatory funnel, and dried under flowing nitrogen and in vacuum (40 °C). A quantity of the bis-NHS diester (0.25 g, 0.213 mmol) was then allowed to react with Jeffamine (0.11 g, 0.22 mmol) in an aqueous solution (10.0 ml) of $NaCO_3$ (30.0 mg, 0.283 mmol) at ambient temperature. The reaction proceeded for 2 h while maintaining the pH at 9.0 (using $NaCO_3$). THF (5.0 ml) was added to the reaction mixture and the solution transferred to a separatory funnel where the polyamide **3** separated out as an oil which was isolated and dried using flowing nitrogen and then in vacuum (40 °C). The yield of the polyamide **3** was about 40% and was further purified by again dissolving in water and adding THF to separate as an oil (Mw= 18,000 Da, PD=1.4 -1.6).

Example 2

Preparation of macromonomer **2**.

PEG_{NH2}3400 (5,00g, 1.47 mmol, 1eq.) was dissolved in acetonitrile (35 ml) in a 100 ml round bottomed flask, placed in an argon atmosphere and kept cold by an ice bath. A two-fold excess of *cis*-aconitic anhydride (0.92g, 5.88 mmol, 4eq) was dissolved in acetonitrile (5 ml) under argon atmosphere. *Cis*-aconitic anhydride solution was slowly added into the cold solution of PEG_{NH2}3400 over an hour, ensuring that addition was slow enough not to cause a colour change in the reaction mixture. The reaction was left to stir in the fridge overnight. The macromonomer was precipitated from the solution with about three times the volume of chilled diethyl ether (120 ml). The precipitate was filtered with vacuum using a glass filter (porosity 3) and further dried in a dissector in vacuum for 30 minutes. The macromonomer **2** was obtained with an isolated yield of 88.1%. Mw_{sec}:..3700 Da. S c indicat s that the mol cular weight was determined by size exclusion chromatography. The GPC standards were PEG.

Preparation of the activated macromonomer **3**.

The macromonomer **2** (2.00g, 0.54 mmol, 1 eq) was dissolved in acetonitrile (25 ml) in a 100 ml round bottom flask, placed in an argon atmosphere and kept cold with an ice bath. A two-fold excess for N-hydroxysuccinimide (NHS) (0.25g, 2.16 mmol, 4 eq.) was dissolved in acetonitrile (2 ml) and added to the cold macromonomer solution. Diisopropyl carbodiimide (DIPC) (0.14g, 1.08 mmol, 2 eq) was also dissolved in acetonitril (2 ml) and slowly added into the reaction solution. The reactions was stirred overnight in the fridge. More acetonitrile (25 ml) was added the next day to dissolve the Diisopropyl urea DIPC precipitate that had been formed during the reaction. The activated macromonomer **3** was then precipitated from the solution with about five times the volume of diethyl ether (250 ml) pre-chilled in an ice bath. The precipitate was filtered with vacuum using a glass filter (porosity 3) and further dried in a dissector in vacuum for 30 minutes. The activated macromonomer **3** was obtained with an isolated yield of 78.5%.

Polymerisation of the activated macromonomer **3** and PEG_{NH2}3400 in aqueous solution.

PEG_{NH2}3'400 (0.7g, 0.20 mmol) was dissolved in pH 9 sodium carbonate solution (17 ml). The resultant solution was added to the activat d macromonomer **3** (0.80g, 0.20 mmol) which had been weighted out in a 50 ml round bottom flask and placed in an ice bath. The pH of the final reaction mixture was checked with universal paper and adjusted slowly to pH 9 with sodium carbonate if necessary. The polymerisation was allowed to take place in the fridge. Aliquots were removed periodically and analysed by SEC) (GPC) to observe the conversion of polymerisation. After 25 hours, the polymer was precipitated using six times the volume of tetrahydrofuran (THF) (100 ml) pre-chilled in an ice bath. Most of the supernatant was discarded and the precipitat was washed again with 150 ml of THF. Cold ether (150 ml) was added to decrease the polarity of he solvent and furth r to purify the polymer. The precipitate was then filtered with vacuum using a glass filter (porosity 3) and further dried in a dissector in vacuum for 30 minutes. Mw_{SEC}>60'000 Da; large polydispersity. The large polydispersity indicates that in the unfractionate or

crude polymer mixture there was also some unreacted prepolymer, dimers, trimers and oligimers in addition to the desired 60 kDa material that was prepared.

The polymer **4** has also been prepared directly from the macromonomer **2** in organic solvent using a coupling reagent only without activating with N-hydroxysuccinimide.

Polymerisation of macromonomer **2** and $PEG_{NH2}3400$ in organic phase.

The macromonmer **2** (2.00g, 0.54 mmol, 1 eq.) was dissolved in acetonitrile (25 ml) in a 100 ml round bottom flask, placed in an argon atmosphere and kept cold with an ice bath. $PEG_{NH2}3400$ (1.83g, 0.54 mmol, 1 eq.) was dissolved in acetonitrile (25 ml) and added to the cold macromonomer solution. DIPC (0.17 ml, 1.08 mmol, 2 eq.) was then slowly added and the polymerisation was allowed to take place in the fridge. Aliquots were removed periodically and analysed by SEC to observe the conversion of polymerisation. The polymer was precipitated after 212 h with six times the volumes of ether (300 ml) pre-chilled in an ice bath. The precipitate was filtered under vacuum with glass filter (porosity 3) and further dried in a dissector under continuous vacuum for 30 minutes. Mw:..7'000<50'000 Da

Degradation study.

An *in vitro* controlled degradation study at 5.5 and 7.4 was carried out on the polyamide obtained via NHS activation. Degradation studies were performed over 7 days at 37°C. In addition, pH 2 was also used but only for 42 hours due to the rapid degradation of the polyamide. These three pH conditions were tested to demonstrate if the polyamides in this invention were indeed pH0sensitive. In particular, pH 7.4 and 5.5 were selected to simulate physiological conditions in the blood circulation and in cell lysosomes respectively. The experiment at pH 2 was done to investigate if the polymer was completely degradable.

The degradation of th polyamide is approximately sev n times fast r at pH 5.5 than at pH 7.4. Over the seven days in solution at pH 7.4, it was found that poly(*cis*-aconitylPEG)s were relatively stable, and their highest molecular weight polymers had experienced only 25% degradation in 7 days. and 70%

degradation at pH 5.5 in 4 days. Figure 2 compares the decrease of the polymer SEC peak for the three pH values tested over 50 h . After 42 h at 37°C, the intensity of the polymer SEC peak had decreased by 8%, 37% and 73% at pH 7.4, 5.5 and 2 respectively.

References:

1. Sepulchre, Marie Odile, Sepulchre, Maurice (Laboratoire Macromoleculaire, Universite P. M. Curie, Paris, F-75252, Fr.). Macromol. Symp., 122 (International Symposium on Polycondensation, Related Processes and Materials, 1996), 291-296 (English) 1997.
2. Barret A, Heath M: Lysosomal enzymes. In: Dingle J, ed. Lysosomes: A Laboratory Handbook, 2nd ed. New York and Oxford: North-Holland Publishing Company, 1977; 19-147.
3. Shen W, Ryser H: Cis-aconityl spacer between daunomycin and macromolecular carriers: a model of pH-sensitive linkage releasing drug from a lysosomotropic conjugate. *Biochim. Biophys. Res. Commun.*, **1981**, 102, 1048-1054.
4. Shen W, Ryser H: Conjugation of poly-L-lysine to albumin and horseradish peroxidase: A novel method of enhancing the cellular uptake of proteins. *Proc. Natl. Acad. Sci.*, **1978**, 75(4), 1872-1876.
5. Gaal D, Hudecz F: Low toxicity and high antitumour activity of daunomycin by conjugation to an immunopotential amphoteric branced polypeptide. *Eur. J. Cancer*, **1998**, 34(1), 155-161.
6. Hudecz F, Gaal D, Kurucz I, Lanyi A, Kovacs A, Mezo G, Rajnavolgyi E, Szekerke M: Carrier design: cytotoxicity and immunogenicity of synthetic branched polypeptides with poly(L-lysine) backbone. *J. Cont. Rel.*, **1992**, 19, 231-244.
7. Franssen E, Koiter J, Kuipers C, Bruins A, Moolenaar F, deZeeuw D, Kruizinga W, Kellogg R, Meijer D: Low molecular weight proteins as carriers for renal drug targeting. preparation of drug-protein conjugates and drug-space derivative and the catabolism in renal cortex homogenates and lysosomal lysates. *J. Med. Chem.*, **1992**, 35, 1246-1259.
8. Wirth M, Fuchs A, Wolf M, Ertl B, Gabor F: Lectin-mediated drug targeting: Preparation, binding characteristics, and antiproliferative activity of wheat germ agglutinin conjugat of doxorubicin on Caco-2 cells. *Pharm. Res.*, **1998**, 15(7), 1031-1037.

9. Al-Shamkhani A, Duncan R: Synthesis, controlled release properties and antitumour activity of alginate *cis*-aconityl daunomycin conjugates. *Int. J. Pharm.*, **1995**, 122, 107-119.

10. Hoes C, Ankone M, Grootoonk J, Feijen J, Struik E v d, Doornmalen A v, Pham D, Man A d, Ettekoven A v, Schlachter I, Boon P, Kaspersen F, Bos E: Synthesis and biological evaluation of immunoconjugates of adriamycin and human IgM linked by poly[N5-(2-hydroxyethyl)-L-glutamine]. *J. Cont. Rel.*, **1996**, 38, 245-266.

11. Yang H, Reisfeld R: Doxorubicin conjugate with a monoclonal antibody directed to a human melanoma-associated proteoglycan suppresses th growth of established tumor xenografts in nude mice. *Proc. Natl. Acad. Sci.*, **1988**, 85, 1189-1193.

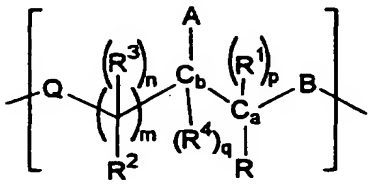
12. Dillman R, Johnson D, Shawler D, Koziol J: Superiority of an acid-labile daunorubicin-monoclonal antibody immunoconjugate compared to fre drug. *Cancer Res.*, **1988**, 48, 6097-6102.

13. Diener E, Diner U, Sinha A, Xie S, Vergidis R: Specific immunosuppression by immunotoxins containing daunomycin. *Science*, **1986**, 231, 148-150.

14. Kirby A, Lancaster P: Structure and efficiency in intramolecular and enzymic catalysis. Catalysis of amide hydrolysis by the carboxy-group of substituted maleamic acids. *J. Chem. Soc. Perk II*, **1972**, 1206-1214.

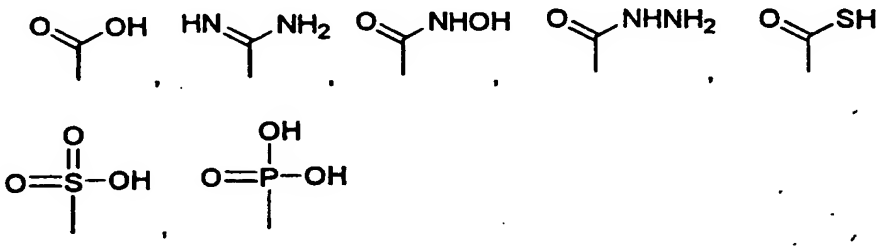
Claims

1. A polymer comprising a polymeric backbone comprising at least one unit having the structure (I),

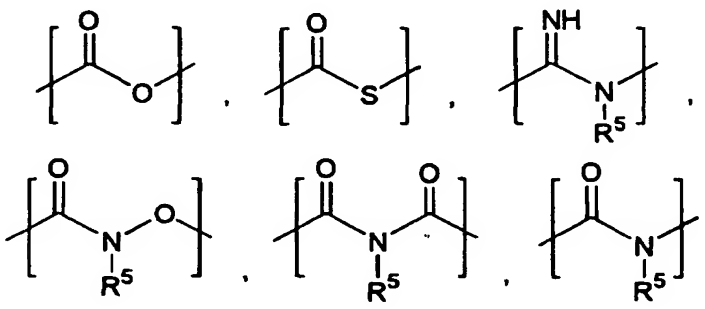


(I)

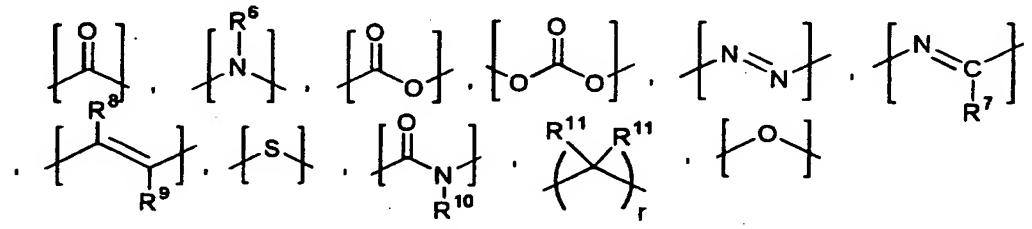
wherein R-R^4 comprise groups selected from the group consisting of H, C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl or any of the group consisting of C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms; R and R^2 or R and R^4 or R and R^1 or R^2 and R^3 may be joined so that with the carbon atom(s) to which they are attached they together form a saturated, partially unsaturated or unsaturated ring system respectively, may have a pendent group which may incorporate a linker unit, (for example a peptide linkage or a unit having the structure (I); A comprises a proton donating moiety selected from the group consisting of



B comprises a hydrolytically labile group and is selected from the group consisting of



wherein each R^5 is individually selected from the group consisting of H, C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl; wherein groups A and B are in a cis-configuration about bond C_a-C_b; m is an integer of 0 to 100, n, p and q are each an integer of 0 or 1; Q comprises 1 or more structures selected from the group consisting of



wherein R^6-R^{11} are individually selected from the same group as defined for group R above and r is an integer between 1 and 5000, and wherein the other components of the polymeric backbone may be other groups having the structure (I), peptide units or degradable polymeric, oligomeric or monomeric units.

2. A polymer according to claim 1, wherein C_a-C_b is a double bond and p and q are each 0.

3. A polymer according to claim 1 or 2, wherein R, R^2 and R^3 are selected from the group consisting of hydrogen, methyl, ethyl or propyl, preferably hydrogen.

4. A polymer according to any preceding claim, wherein A is a carboxylic acid group.

5. A polymer according to any preceding claim, wherein B comprises an amide bond.

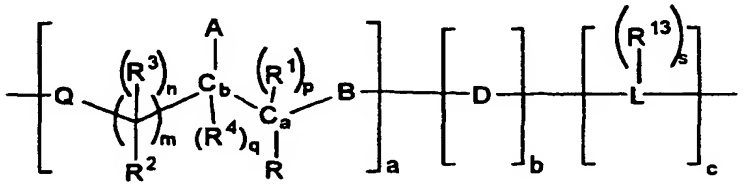
6. A polymer according to any preceding claim, wherein Q comprises a carbonyl funtionality.

7. A polymer according to any preceding claim, wherein the polymeric backbone additionally comprises polymers selected from the group consisting of acrylic polymers, alkylene polymers, urethane polymers, amide polymers (including polypeptides), polysaccharides and ester polymers.

8. A polymer according to any preceding claim, wherein the polymeric backbon comprises polymers selected from th group consisting of d rivatised polyethyleneglycol and copolymers of hydroxyalkyl(meth)acrylamid , most preferably amine d rivatised

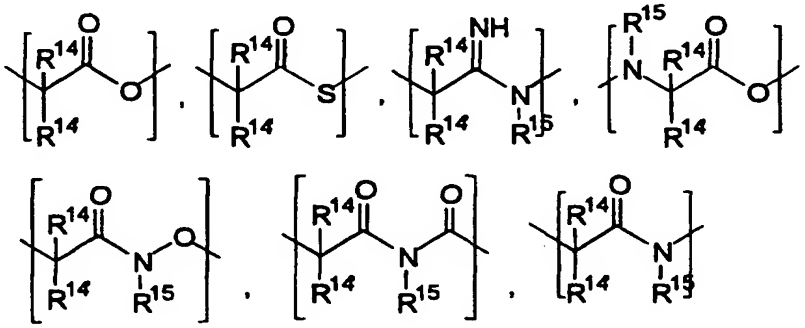
polyethyleneglycol or hydroxypropylmethacrylamide-methacrylic acid copolymers or amide or ester derivatives thereof.

9. A polymer according to any preceding claim, wherein the polymeric backbone comprises the structure (II)

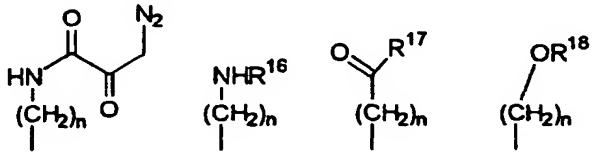


(II)

wherein A, B, Q, R-R^4, m, n, p and q are as defined in any preceding claim; L is a polymeric, oligomeric or copolymeric bridging group which comprises polymer selected from the group consisting of acrylic polymers, alkylene polymers, urethane polymers, polyethylene glycols, polyamides, polysaccharides and polyesters; a is an integer of 1 to 100000, b and c are integers of 0 to 100000 and s is an integer of 0 to 100; D comprises one or more structures individually selected from the group consisting of;



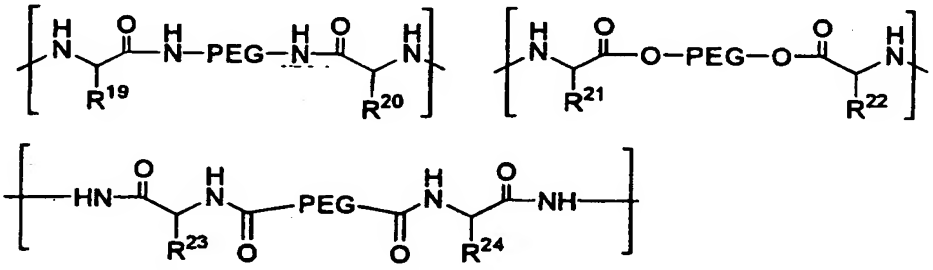
wherein R^{14} and $R^{14'}$ comprise groups individually selected from the same groups as defined for R or may comprise a structure selected from the group consisting of



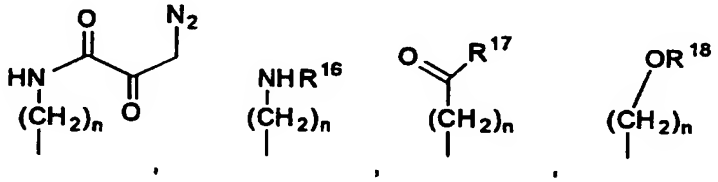
wherein n is an integer of 0-100, R^{15} is selected from the group consisting of hydrogen and C_1-C_6 alkyl, R^{16} to R^{18} are individually s lected from the group consisting of H, C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_5-C_{18}

cycloalkyl or is selected from the group consisting of C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms, a pendent group comprising a linker unit, for example a peptide linkage or a unit having the structure (I) or a leaving group; R^{13} is selected from the group consisting of H, C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_5-C_{18} cycloalkyl or is selected from the group consisting of C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms, R^{13} optionally incorporating a linker unit, for example a peptide linkage or a unit having the structure (I).

10. A polymer according to claim 9, wherein L comprises amine derivatised polyethyleneglycol, most preferably a structure selected from the group consisting of



wherein PEG is polyethyleneglycol, R^{19}-R^{24} optionally incorporates a pendent group comprising a cleavable linker unit, and may additionally comprise groups individually selected from the same groups as defined for R or may comprise a structure selected from the group consisting of



wherein n and R^{16} to R^{18} and R^{16} to R^{18} are as defined in claim 9.

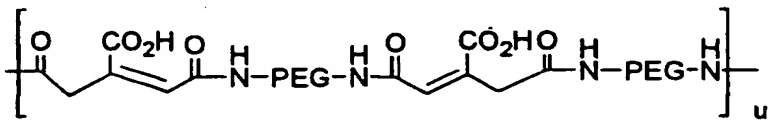
11. A polymer according to claim 9 or 10, wher in s is an integer of 1 to 10, preferably 1.

12. A polymer according to claim 9, 10 or 11, wherein at least one of R^{14} to R^{24} incorporates a cleavable bond, preferably a group (I) or one or more peptide bonds.

13. A polymer according to any preceding claim, wherein the polymer is conjugated to a bioactive agent, preferably an anti cancer agent, most preferably, doxorubicin, daunomycin or taxol.

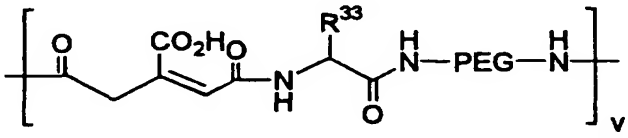
14. A polymer according to any preceding claim, wherein the molecular weight is in the range 0.5kDa-400kDa.

15. A polymer according to any preceding claim, having the structure



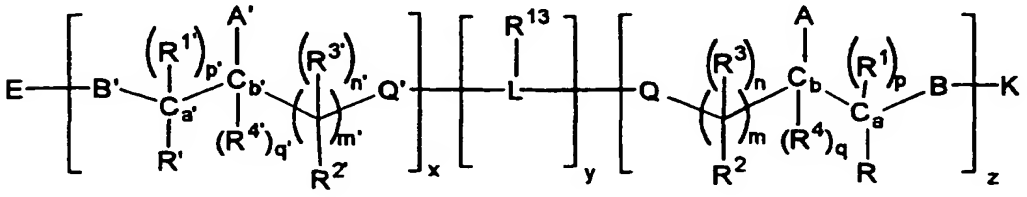
wherein PEG is a polyethylene glycol group, or derivative thereof, having a molecular weight in the range 500 Da-100kDa and u is an integer in the range of 1-10000.

16. A polymer according to any of claims 1 to 14, having the structure



wherein PEG is a polyethylene glycol group having a molecular weight in the range 500 Da-100kDa or derivative thereof, and u is an integer in the range of 1-10000.

17. A prepolymer comprising the structure



(III)

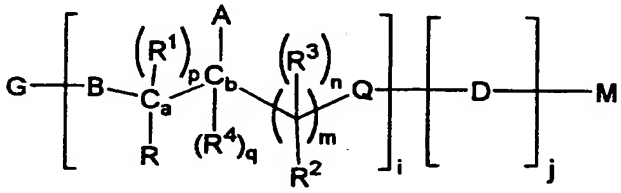
wherein A, B, Q, R-R^3, m, n, p and q are as defined in any preceding claim; R^{13} and L are as defined in any of claims 9 to 16; A', B', Q' $R^{1'}$-$R^{4'}$, m', n', p', and q' are selected from the groups as defined for A, B, Q, R^1- R^4 m, n, p and q respectively; E and K ar selected from the group consisting of hydrog n,

an activating group or a protecting group and may be the same or different; z is an integer of 1 to 100, y is an integer of 0 to 10 and x is an integer of 0 to 100.

18. A prepolymer according to claim 17, wherein z is 1, y is 1 and x is 1.

19. A prepolymer according to claim 17 or 18, wherein B and B' comprise a carboxyl group and E and K are selected from the group consisting of hydrogen, N-succinimidyl pentachlorophenyl, pentaflourophenyl, para-nitrophenyl, dinitrophenyl, N-phthalimido, N-norbornyl, cyanomethyl, pyridyl, trichlorotriazine, 5-chloroquinoline, preferably hydrogen or N-succinimidyl.

20. A prepolymer comprising the structure (IV)



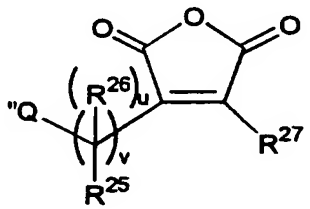
(IV)

wherein A, B, Q, R-R^4, m, n, p and q are as defined in any preceding claim; D si as defined in any of claims 9 to 16; G and M are selected from the group consisting of hydrogen, an activating group or a protecting group, i and j are integers of 1 to 10.

21. A prepolymer according to claim 20, wherein i is 1 and j is 1.

22. A prepolymer according to claim 20 or 21, wherein B and D comprise carboxylic acid groups and G and M are selected from the group consisting of hydrogen, N-succinimidyl pentachlorophenyl, pentaflourophenyl, para-nitrophenyl, dinitrophenyl, N-phthalimido, N-norbornyl, cyanomethyl, pyridyl, trichlorotriazine, 5-chloroquinoline, preferably hydrogen or N-succinimidyl.

23. A process for preparing a polymer, copolymer or prepolymer comprising reacting at least one compound having the structure (V)



(V)

wherein R^{25}, R^{26} and R^{27} are selected from the group as defined for R; Q" is selected from the group consisting of carboxylic acid, primary or secondary amine carbonyl; u is an integer of 0 or 1, v is an integer of 1 to 100, R^{27} and R^{25} may be attached to form part of a C_3 - C_{12} ring system which may have more than one unsaturated bond and may be aromatic; with at least one compound selected from the group consisting of J and $R^{13}LNHR^{28}$, wherein L and R^{13} groups are as defined above and R^{28} is selected from the same group as defined for R and may be the same or different, J is a compound having at least one primary or secondary amine and a carboxylic acid group and a pendent group incorporating a cleavable bond.

23. A method of selectively degrading a polymer comprising the steps of:
    a) introducing a polymer as comprising a structure (I) or (II) as defined in any preceding claim, to an environment having a pH of less than 6.5,
    b) cleaving said polymer.

24. A method for releasing a bioactive agent comprising the steps of
    a) introducing a conjugate comprising a structure (I) or (II) as defined in any preceding claim, and a bioactive agent to an environment having a pH of less than 6.5,
    c) cleaving the bioactive agent from the linker group by acid or enzymic hydrolysis,
    d) optionally additionally cleaving the polymer by acid or enzymic hydrolysis.

25. A composition comprising at least one polymer as defined in any of claims 1 to 16 and a carrier.

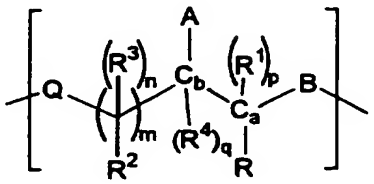
26. A composition comprising at least one polymer as defined in any of claims 1 to 16 and a pharmaceutically acceptable excipient.

27. Use of a polymer as defined in any of claims 1 to 16 as a pharmaceutical excipient.

Abstract

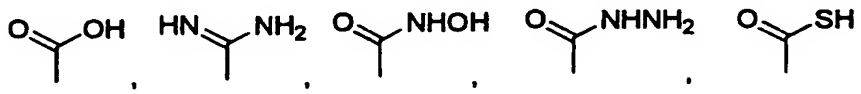
A polymer comprising:

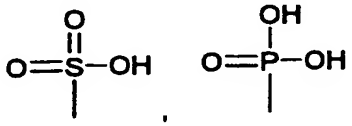
a polymeric backbone backbone comprising at least one unit having the structure (I),



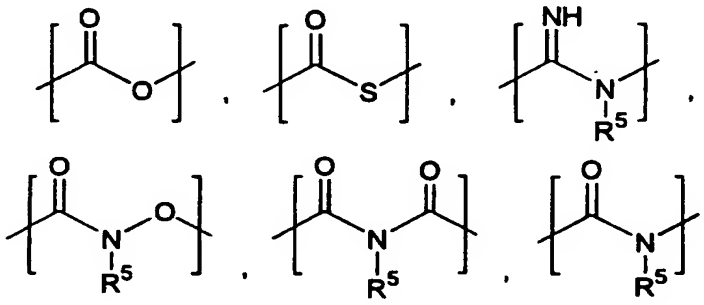
(I)

wherein R-R^4 comprise groups selected from the group consisting of H, C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl or any of the group consisting of C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms; R and R^2 or R and R^4 or R and R^1 or R^2 and R^3 may be joined so that with the carbon atom(s) to which they are attached they together form a saturated, partially unsaturated or unsaturated ring system respectively, may have a pendent group which may incorporate a linker unit, (for example a peptide linkage) or a unit having the structure (I); A comprises a proton donating moiety selected from the group consisting of

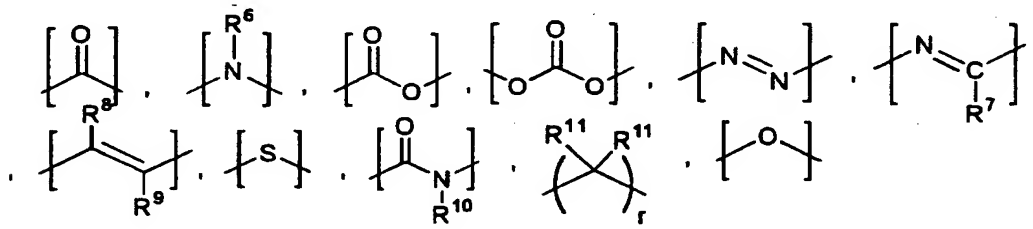




B comprises a hydrolytically labile group and is selected from the group consisting of



wherein each R^5 is individually selected from the group consisting of H, C_1-C_{12} alkyl, C_6-C_{18} aryl, C_7-C_{18} aralkyl, C_6-C_{18} cycloalkyl; wherein groups A and B are in a cis-configuration about bond C_a-C_b; m is an integer of 0 to 100, n, p and q are each an integer of 0 or 1; Q comprises 1 or more structures selected from the group consisting of



wherein R^6-R^{11} are individually selected from the same group as defined for group R above and r is an integer between 1 and 5000, preferably 1 to 10, most preferably 1 to 6; methods for the production, and uses thereof.

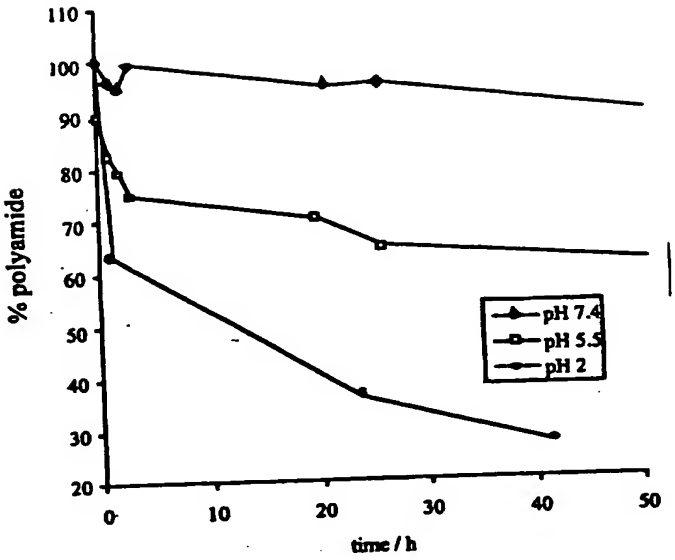

% polyamide
time / h
pH 7.4
pH 5.5
pH 2
110
100
90
80
70
60
50
40
30
20
0
10
20
30
40
50

Figure 1